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FOR

**AGENTS THAT STIMULATE THERAPEUTIC ANGIOGENESIS AND
TECHNIQUES AND DEVICES THAT ENABLE THEIR DELIVERY**

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AGENTS THAT STIMULATE THERAPEUTIC ANGIOGENESIS AND TECHNIQUES AND DEVICES THAT ENABLE THEIR DELIVERY

BACKGROUND

Field

[0001] This invention relates to resolving ischemia by inducing formation of blood vessels through therapeutic angiogenesis.

Relevant Art

[0002] A major component of morbidity and mortality attributable to cardiovascular disease occurs as a consequence of the partial or complete blockage of vessels carrying blood in the coronary and/or peripheral vasculature. When such vessels are partially occluded, lack of blood flow causes ischemia to the muscle tissues supplied by such vessel, consequently inhibiting muscle contraction and proper function. Total occlusion of blood flow causes necrosis of the muscle tissue.

[0003] Blood vessel occlusions are commonly treated by mechanically enhancing blood flow in the affected vessels. Such mechanical enhancements are often provided by employing surgical techniques that attach natural or synthetic conduits proximal and distal to the areas of occlusion, thereby providing bypass grafts, or revascularization by various means to physically enlarge the vascular lumen at the site of occlusion. These revascularization procedures involve such devices as balloons, endovascular knives (atherectomy), and endovascular drills. The surgical approach is accompanied by significant morbidity and even mortality, while the angioplasty-type processes are complicated by recurrent stenoses in many cases.

[0004] In some individuals, blood vessel occlusion is partially compensated by natural processes, in which new vessels are formed (termed "angiogenesis") and small vessels are enlarged (termed "arteriogenesis") to replace the function of the impaired vessels. These new conduits may facilitate restoration of blood flow to the deprived tissue, thereby constituting "natural bypasses" around the occluded vessels. However, some individuals are unable to generate sufficient collateral vessels to adequately compensate for the diminished blood flow caused by cardiovascular disease. Accordingly, it would be desirable to provide a method and apparatus for delivering agents to help stimulate the natural process of therapeutic angiogenesis to compensate for blood loss due to an occlusion in a coronary and peripheral arteries in order to treat ischemia.

SUMMARY

[0005] A method is disclosed. In one embodiment the method includes positioning a delivery device such as a catheter at a location in a blood vessel and advancing the delivery device a distance into a wall of the blood vessel to a treatment site. A treatment agent is then introduced through the delivery device to the treatment site. The method also includes identifying a treatment site based on imaging a thickness of a portion of the wall of the blood vessel. In the example of introducing a treatment agent that would stimulate a therapeutic angiogenesis response, the method describes a technique for accurately delivering a treatment agent into the wall of the blood vessel or beyond the wall of the blood vessel as the particular situation may dictate. The method utilizes imaging of a thickness of the wall of a blood vessel to accurately place the treatment agent. Suitable imaging techniques include, but are not limited to, ultrasonic imaging, optical imaging, and magnetic resonance imaging.

[0006] In another embodiment, a method includes introducing a treatment agent in a sustained release composition or carrier. Treatment agents that can sustain their effectiveness for a period of up to one to ten weeks, preferably two to eight weeks, offer maximum benefit for the stimulation of therapeutic angiogenesis. Methods of inducing coronary or peripheral therapeutic angiogenesis by local delivery of sustained release treatment agents using percutaneous devices are described. Such devices may be intraventricular (coronary) or intravascular (coronary and peripheral).

[0007] In another embodiment, a method includes placing a treatment agent in or around a blood vessel or other tissue that stimulates therapeutic angiogenesis by inducing an inflammation response in tissue.

[0008] In still another embodiment, a sustained-release composition comprising a treatment agent in a form suitable for transvascular delivery is described. Also, a composition comprising a carrier including a treatment agent and an opsonin-inhibitor coupled to the carrier.

[0009] In a further embodiment, an apparatus is described that allows the accurate introduction of a treatment agent in or around a blood vessel. The apparatus includes, for example, a catheter body capable of traversing a blood vessel and a dilatable balloon assembly coupled to the catheter body comprising a balloon having a proximal wall. A needle body is disposed within the catheter body and comprises a lumen having dimensions suitable for a needle to be advanced there through. The needle body includes an end coupled to the proximal wall of the balloon. The apparatus also includes an imaging body disposed within the catheter body and comprising a lumen having a dimension suitable for a portion of an imaging device to be advanced there through. The apparatus further includes a portion of an imaging device disposed within the imaging body adapted to generate imaging signals of the blood vessel, including imaging signals of a thickness of the wall of a blood vessel. An

apparatus such as described is suitable for accurately introducing a treatment agent at a desired treatment site in or around a blood vessel.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **Figure 1** schematically illustrates a perspective and cross-section view of a blood vessel:

[0011] **Figure 2** schematically illustrates a planar cross-sectional view of components of a coronary artery network;

[0012] **Figure 3** is a simplified cross-sectional view of an embodiment of a substance delivery apparatus in the form of a catheter assembly having a balloon and a therapeutic substance delivery assembly;

[0013] **Figure 4** schematically illustrates a planar cross-section of the substance delivery apparatus of **Figure 3** through line A-A';

[0014] **Figure 5** schematically illustrates a planar cross-section of the substance delivery apparatus of **Figure 3** through line B-B';

[0015] **Figure 6** schematically illustrates a cross-sectional view of the distal section of the substance delivery apparatus of **Figure 3** with the balloon in an undeployed configuration;

[0016] **Figure 7** schematically illustrates a cross-sectional view of the distal section of the substance delivery apparatus of **Figure 3** with the balloon in a deployed configuration;

[0017] **Figure 8** schematically illustrates an optical imaging system for use in a substance delivery apparatus such as a catheter assembly;

[0018] **Figure 9** schematically illustrates a cross-sectional side view of components of an alternative catheter assembly including an optical imaging system.

[0019] **Figure 10** schematically illustrates the left coronary artery network having a catheter assembly introduced therein; and

[0020] **Figure 11** presents a block diagram for introducing a treatment agent.

[0021] The features of the described embodiments are specifically set forth in the appended claims. However, the embodiments are best understood by referring to the following description and accompanying drawings, in which similar parts are identified by like reference numerals.

DETAILED DESCRIPTION

[0022] In connection with the description of the various embodiments, the following definitions are utilized:

[0023] "Therapeutic angiogenesis" refers to the processes of causing or inducing angiogenesis and arteriogenesis.

[0024] "Angiogenesis" is the promotion or causation of the formation of new blood vessels in the ischemic region.

[0025] "Arteriogenesis" is the enlargement of pre-existing collateral vessels. The collateral vessels allow blood to flow from a well-perfused region of the vessel into the ischemic region.

[0026] "Ischemia" is a condition where oxygen demand of the tissue is not met due to localized reduction in blood flow caused by narrowing or occlusion of one or more vessels. Narrowing of arteries such as coronary arteries or their branches, is most

often caused by thrombosis or via deposits of fat, connective tissue, calcification of the walls, or restenosis due to abnormal migration and proliferation of smooth muscle cells.

[0027] "Occlusion" is the total or partial obstruction of blood flow through a vessel.

[0028] "Treatment agent" includes agents directed to specific cellular binding sites (e.g., receptor binding treatment agents) and agents that induce inflammation.

[0029] "Specific binding treatment agent" or "receptor binding treatment agent" includes a protein or small molecule that will induce and/or modulate a therapeutic angiogenic response through interaction with a specific binding site (e.g., a binding within a cell or on a cell surface). Representative treatment agents include, but are not limited to, vascular endothelial growth factor (VEGF) in any of its multiple isoforms, fibroblast growth factors, monocyte chemoattractant protein 1 (MCP-1), transforming growth factor beta (TGF-beta) in any of its multiple isoforms, transforming growth factor alpha (TGF-alpha), lipid factors, hypoxia-inducible factor 1-alpha (HIF-1-alpha), PR39, DEL 1, nicotine, insulin-like growth factors, placental growth factor (PIGF), hepatocyte growth factor (HGF), estrogen, follistatin, proliferin, prostaglandin E1, prostaglandin E2, cytokines, tumor necrosis factor (TNF-alpha), erythropoietin, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), angiogenin, hormones, and genes that encode such substances.

[0030] "Non-specific treatment agent" includes, as described in more detail herein, various agents that induce inflammation.

[0031] "Carrier" includes a matrix that contains one or more treatment agents. A suitable carrier may take the form of a nanoparticle (e.g., nanosphere) or microparticle (e.g., microsphere) as the situation may dictate.

[0032] Referring to **Figure 1**, a non-diseased artery is illustrated as a representative blood vessel. Artery 100 includes an arterial wall having a number of layers. Innermost layer 110 is generally referred to as the intimal layer that includes the endothelium, the subendothelial layer, and the internal elastic lamina. Medial layer 120 is concentrically outward from intimal layer 110 and bounded by external elastic lamina and adventitial layer 130 is the outermost layer. There is no external elastic lamina in a vein. Medial layer 120 (in either an artery or vein) primarily consists of smooth muscle fibers and collagen. Beyond medial layer 120 and adventitial layer 130 lies the extravascular tissue including, adjacent adventitial layer 120 (and possibly including a portion of adventitial layer 120), area 140 referred to as peri-adventitial site (space) or area. Areas radially outward from a peri-adventitial space include connective tissue such as adipose tissue that is most likely located, in terms of areas around the heart, toward the epicardial surface of the heart and myocardial tissue composed of muscle fibers.

[0033] **Figure 2** illustrates components of a coronary artery network. In this simplified example, vasculature 150 includes left anterior descending artery (LAD) 160, left circumflex artery (LCX) 170 and right coronary artery (RCA) 180. Sites 190A, 190B, and 190C are preferably in the peri-adventitial space or radially outward from the peri-adventitial space (e.g., in adipose or myocardial tissue). Occlusion 185 is shown in LCX 170. Occlusion 185 limits the amount of oxygenated blood flow through LCX 170 to the myocardium that it supplied, resulting in ischemia of this tissue.

[0034] To improve the function of the artery network, it is generally desired to either remove occlusion 185 (for example through an angioplasty procedure), bypass occlusion 185 or induce therapeutic angiogenesis to makeup for the constriction and provide blood flow to the ischemic region (e.g., downstream of occlusion 185). **Figure**

2 shows therapeutic angiogenesis induced at sites 190A (associated with LCX 170); 190B (associated with LAD 160); and 190C (associated with RCA 180). By inducing therapeutic angiogenesis at sites 190A, 190B, and 190C, permanent revascularization of the network is accomplished, thus compensating for reduced flow through LCX 170. The following paragraphs describe compositions, techniques and an apparatus suitable for inducing therapeutic angiogenesis.

A. Specific Binding Treatment Agents

[0035] In one embodiment, therapeutic angiogenesis is induced and modulated by locally delivering a treatment agent in a sustained-release carrier. The sustained-release carrier comprising a treatment agent may be strategically placed, for example, along an occlusion to produce an angiogenic concentration gradient to encourage the specific directional growth or expansion of collateral vessels. For example, in reference to **Figure 2**, treatment agents placed at zone 190A, above (as viewed) occluded vessel LCX 170 are selected such that, while up-stream, a therapeutic angiogenic or arteriogenic response will encourage growth of collaterals around occlusion 185 meeting up with LCX 170 down-stream of the occlusion. Similarly, a treatment agent strategically placed at a location in a region near to left coronary artery 160 (e.g., region 190B) will encourage bridging of collateral vessels, in this case, between left coronary artery 160 and LCX 170. Similar encouragement and bridging may be obtained by strategically placing a treatment agent at a region of RCA 180 (such as region 190C). While the application of therapeutic angiogenesis to alleviating ischemia resulting from a flow limiting obstruction in the LCX is described, those familiar with the art will appreciate that the method described is applicable to the treatment of flow limiting obstructions in other coronary vessels and in the peripheral vasculature.

[0036] Suitable treatment agents include specific binding or receptor binding treatment agents. Suitable sustained-release carriers encapsulating the specific binding agents may take the form of polymer nanoparticles or microparticles, typically in the form of nanospheres or microspheres, having an average particle size less than 100 microns (μm) and preferably less than about 10 μm to, in one aspect, enable delivery through a catheter equipped with an injection needle. Sustained release of treatment agents for a period of up to one to ten weeks, preferably up to two to eight weeks is believed to offer maximum benefit for the stimulation of therapeutic angiogenesis. In another embodiment, the sustained release of treatment agents over a period of one day or longer is preferred. The loading of the receptor binding treatment agent in the sustained release carrier is in the range of about 0.5 percent to about 30 percent weight by volume (w/v), and the total dose of the receptor binding treatment agent delivered to the treatment location is in the range of about 1 microgram (μg) to about 1 gram (g).

[0037] Sustained release microparticle formulations with different release rates may be delivered in combination to achieve multi-modal release profiles over a period of time.

B. Non-Specific Treatment Agents

[0038] As stated above, specific binding or receptor binding treatment agents can induce therapeutic angiogenesis. One embodiment of another suitable treatment agent that will induce and/or modulate a therapeutic angiogenic response is an inflammation-inducing agent. Studies have shown that tissue, including blood vessels, respond to injury induced by implanting foreign materials in three broad phases. The first phase is characterized by minimal inflammatory reaction, with the presence of a few lymphocytes, plasma cells, monocytes, and polymorphonuclear leukocytes. The response to injury in this first phase is determined primarily by the extent of injury caused, for example, by a needle of a needle catheter contacting a blood vessel and the

volume of therapeutic substance (e.g., treatment agent) injected to the site of interest. The second response to injury phase is characterized by a predominance of monocytes and macrophages. In the case of biodegradable implants, the duration of this second phase is determined by the rate of biodegradation of the carrier. During this phase, monocytes differentiate into macrophages at the site of injury and the macrophages themselves fuse into foreign body "giant" cells. Fibroblast infiltration and neoangiogenesis are also observed at this stage. For biodegradable implants, there is a third response to injury phase, characterized by the breakdown of the biodegradable material. In this phase, macrophages predominate at the site of implantation. The extent of inflammation and the concentration of monocyte/macrophages at the implantation site reaches a peak at this third phase. Monocyte accumulation and activation is thought to be a potent means of inducing therapeutic angiogenesis

[0039] In one embodiment, ischemic regions supplied by a blood vessel such as ischemic region caused by a lesion in the LCX 170 in **Figure 2** may be treated by implantation of an inflammation-inducing agent (a "non-specific" agent) optionally combined with or contained in (encapsulated) a sustained-release carrier. The implantation may be accomplished non-invasively through, for example, catheter-based technologies, minimally invasively, or in conjunction with surgical procedures. The extent and duration of inflammation is dependent on the non-specific agent being implanted. A combination of agents may be implanted to modulate the extent of inflammation over a period of time, which is typically on the order of about two weeks to about eight weeks.

[0040] Suitable inflammation-inducing agents include, but are not limited to, (1) bioresorbable inorganic compounds such as sol gel particles and calcium phosphate glass comprising iron; (2) fibrin, gelatin, low molecular weight hyaluronic acid, and chitin; (3) bacterial polysaccharides; (4) metals; and (5) certain other polymers (which

themselves may function as both treatment agent and carrier, including a sustained-release carrier) including bioresorbable polymers such as polycaprolactone (PCL), polyhydroxybutyrate-valerate (PHBV), poly(oxy)ethylene (POE), and non-bioresorbable polymers such as polyurethanes and silicones. The inflammation-inducing treatment agent may be combined as a composition with one or more other specific binding or receptor binding treatment agents that are believed to induce therapeutic angiogenesis such as growth factors.

[0041] Representative examples of inflammation-inducing treatment agents that may be combined, in one embodiment, with a sustained release carrier include the following.

[0042] Silica sol gel particles, such as manufactured by Bioxid LTD OY of Turku, Finland, are bioresorbable inorganic compounds that can be pro-inflammatory on their own and also serve as a drug eluting reservoir for other pro-inflammatory agents (e.g., lipopolysaccharides (LPS), chitin, etc.). Calcium-phosphate glass containing iron will degrade in a humid environment as a function of the iron composition, resulting in an absorbable glass. One example of absorbable glass is made by MOSCI, Inc. of Rolla, Missouri. The absorbable glass may induce controlled inflammation by the physical dimension of the degradation product. A combination of PLGA coated (with or without activation) or partially coated absorbable glass may be employed to modulate the degradation rate of different species.

[0043] Chitin is a polysaccharide derived principally from crab shells, and shows a pro-inflammatory reaction. Micronized chitin can be incorporated into microspheres or disbursed into a polymer system such as described above to enhance the inflammatory action of treatment agent of microspheres or precipitated polymers. The micronized chitin can also be disbursed in a gel that may then be extruded via a needle catheter to a desired treatment location (within the vascular or myocardium).

Gelatin (a partially degraded form of collagen) and fibrin may be utilized in a similar manner.

[0044] The outer membranes of gram-negative bacteria containing lipopolysaccharides (LPS) can be pro-inflammatory. Isolation of LPS and incorporation into degradable microspheres can enhance the inflammatory reaction of the microspheres and provide a more potent angiogenic action.

[0045] The cell walls of blood vessels are typically rich in glycocalyx and other specific antigens. Systemic immune response may be upregulated by administration of vaccines or denatured proteins such as Ab, Fb, etc. In another embodiment, the localized introduction (e.g., through a catheter) of vaccines or certain denatured proteins may be used in combination with, for example, inflammatory-inducing treatment agents to potentiate the controlled inflammatory effect

[0046] Particles of metal such as gold (Au) and titanium (Ti) are known to induce inflammation and activate monocytes. These particles may be injected as a suspension at a local site of interest via, for example, a needle catheter. To amplify an effect, such thermally conductive particles can be heated with, for example, using a 900 to 1200 nanometer (nm) range remote source of radio frequency energy to further cause controlled damage to the tissue resulting in inflammation and promoting therapeutic angiogenesis. 10 to 100 nanometer (nm) spherical particles are shown to have this remote activatable heating effect.

C. Methods of Forming Sustained Release Particles

[0047] In the previous paragraphs, both specific binding treatment agents and non-specific binding treatment agents have been described in conjunction with promoting therapeutic angiogenesis. Such promotion is encouraged, in one embodiment, by delivering the treatment agent in or with a sustained-release carrier.

Suitable materials for sustained-release carriers include, but are not limited to, encapsulation polymers such as poly (L-lactide), poly (D,L-lactide), poly (glycolide), poly (lactide-co-glycolide), polycaprolactone, polyanhydride, polydiaxanone, polyorthoester, polyamino acids, or poly (trimethylene carbonate), and combinations thereof. To form a sustained-release carrier composition of, for example, microparticles or nanoparticles (e.g., microspheres or nanospheres) comprising one or more treatment agents including a non-specific treatment agent and/or a specific binding agent, the following techniques may be used.

1. Solvent Evaporation

[0048] In this method, the polymer is dissolved in a volatile organic solvent such as methylene chloride. The treatment agent is then added to the polymer solution either as an aqueous solution containing an emulsifying agent such as polyvinyl alcohol (PVA), or as a solid dispersion, and stirred, homogenized or sonicated to create a primary emulsion of protein in the polymer phase. This emulsion is stirred with an aqueous solution containing an emulsifying agent such as PVA to create a secondary emulsion of treatment agent containing polymer in the aqueous phase. This emulsion is stirred in excess water, optionally under vacuum to remove the organic solvent and harden the particles. The hardened particles are collected by filtration or centrifugation and lyophilized. A desired particle size (e.g., microparticle or nanoparticle) may be selected by varying the preparation conditions (e.g., viscosity of the primary emulsion, concentration of the treatment agent, mixing (shear) rate, etc.). The particles tend to adopt a spherical shape in response to minimizing surface tension effects.

2. Coacervation:

[0049] In this method, a primary emulsion of treatment agent in an aqueous phase is formed as in the solvent evaporation method. This emulsion is then stirred

with a non-solvent for the polymer, such as silicone oil to extract the organic solvent and form embryonic particles of polymer with trapped treatment agent. The non-solvent is then removed by the addition of a volatile second non-solvent such as heptane, and the particles hardened. The hardened particles are collected by filtration or centrifugation and lyophilized. Again, the particle size may be selected as described above with reference to solvent evaporation.

3. Spray Drying:

[0050] In this method, the treatment agent, formulated as lyophilized powder is suspended in a polymer phase consisting of polymer dissolved in a volatile organic solvent such as methylene chloride. The suspension is then spray dried to produce polymer particles with entrapped treatment agent. The particle size may be selected as described above with reference to solvent evaporation.

4. Cryogenic process:

[0051] In this method, the treatment agent, formulated as lyophilized powder is suspended in a polymer phase consisting of polymer dissolved in a volatile organic solvent such as methylene chloride. The suspension is sprayed into a container containing frozen ethanol overlaid with liquid nitrogen. The system is then warmed to -70°C to liquify the ethanol and extract the organic solvent from the treatment agent particles. The hardened microspheres are collected by filtration or centrifugation and lyophilized.

5. In situ Process:

[0052] Sustained release carriers (e.g., microparticles and/or nanoparticles) may be formed before introduction (e.g., injection) into the blood vessel as described above, or they may be formed in situ. One way to form such particles in situ is by co-

desolving a treatment agent and a matrix forming polymer in a water miscible solvent such as dimethyl sulfoxide (DMSO), N-methylpyrrolidone (NMP), ethanol or glycofural and injecting the solution at the site of treatment with, for example, a catheter to precipitate out polymer particles. Several polymer solutions, each consisting of a polymer formulation with a different degradation rate can be injected in sequence to precipitate out a mixed population of polymer particles, in order to obtain a multi-modal release profile.

6. Example of Loading and Dose for Inducing/Modulating Therapeutic Angiogenesis

[0053] As noted above, one example of the preparation of nanoparticles (e.g., nanospheres) or microparticles (e.g., microspheres) suitable for use in therapeutic angiogenesis is in the form of a solution. Nanoparticles or microparticles may be loaded with specific or non-specific agents in the range of 0.5-30 percent w/v. In the case of inflammatory agents, loading may be as high as 100 percent w/v. A suitable dose may be calculated as follows:

[0054]
$$\text{DOSE} = \text{number of injections} \times \% \text{ suspension of nano- and/or microparticles} \left[\frac{\text{weight of nano- and/or microparticles}}{\text{volume of solution}} \right] \times \text{volume of solution} \times \% \text{ loading} \left[\frac{\text{weight of agent}}{\text{weight of nano- and/or microparticles}} \right].$$

[0055] Using an inflammatory treatment agent such as gold particles as an example, loading may be 100 percent. In 0.2 ml solution five percent w/v of particles provides for maximal dose of 10 micrograms of material per injection. The number of injections is determined by an operator. The total dose is in the range of 1 microgram to 1 gram. It is to be appreciated that the optimal dose may be determined in a relevant animal model of ischemia by delivering the nano- and/or microparticle suspension through a needle catheter or simply by injecting during open-heart procedure and generating a dose-response curve.

D. Compositions Having a Particle Size of 10 Microns or Less

[0056] Treatment agents, including treatment agents combined with a carrier (e.g., a sustained release carrier), having a particle size greater than approximately 10 microns have the potential, when introduced into the arterial vascular system, of being trapped in the capillary bed. Trapping large numbers of microparticles in the capillary bed could result in ischemia. Treatment agent compositions having particle diameters less than about 10 microns, however, are rapidly phagocytosed, resulting in reduced availability of the treatment agent at target sites, where, for example, sustained-released of the treatment agent may be desired in a certain therapeutic concentration range.

[0057] Regarding phagocytosis, when a foreign material is implanted into a host tissue, the first event to occur at the tissue-material interface is the adsorption of plasma proteins from blood onto the surface of the foreign material. Opsonins are plasma proteins, such as complement and immunoglobulin, that adhere to foreign materials such as nanoparticles and facilitate their phagocytosis through the recognition of the adsorbed opsonins by macrophages of the reticulo-endothelial system. Microspheres larger than about 10 microns are also opsonized, but are generally considered too large to be phagocytosed.

[0058] In one embodiment, the treatment agent compositions suitable for therapeutic angiogenesis are rendered resistant to phagocytosis by inhibiting opsonin protein adsorption to the composition particles. In this regard, treatment agent compositions including sustained release carriers comprise particles having an average diameter of up to about 10 microns are contemplated.

[0059] One method of inhibiting opsonization and subsequent rapid phagocytosis of treatment agents is to form a composition comprising a treatment agent disposed within a carrier (e.g., a sustained release carrier) and to coat the carrier with

an opsonin inhibitor. One suitable opsonin-inhibitor includes polyethylene glycol (PEG) which creates a brush-like steric barrier to opsonization. PEG may alternatively be blended into the polymer constituting the carrier, or incorporated into the molecular architecture of the polymer constituting the carrier, as a copolymer, to render the carrier resistant to phagocytosis. Examples of preparing the opsonin-inhibited microspheres include the following.

[0060] For the encapsulation polymers, a blend of a polyalkylene glycol such as polyethylene glycol (PEG), polypropylene 1,2-glycol or polypropylene 1,3-glycol is co-dissolved with an encapsulating polymer in a common organic solvent during the carrier forming process. The percentage of PEG in the PEG/encapsulating polymer blend is between five percent and 60 percent by weight. Other hydrophilic polymers such as polyvinyl pyrrolidone, polyvinyl alcohol, or polyoxyethylene-polyoxypropylene copolymers can be used in place of polyalkylene glycols, although polyalkylene glycols and more specifically, polyethylene glycol is generally preferred.

[0061] Alternatively, a diblock or triblock copolymer of an encapsulating polymer such as poly (L-lactide), poly (D,L-lactide), or poly (lactide-co-glycolide) with a polyalkylene glycol may be prepared. Diblocks can be prepared by: (i) reacting the encapsulating polymer with a monomethoxy polyalkylene glycol such as PEG with one protected hydroxyl group and one group capable of reacting with the encapsulating polymer, (ii) by polymerizing the encapsulating polymer on to the monomethoxy polyalkylene glycol such as PEG with one protected group and one group capable of reacting with the encapsulating polymer; or (iii) by reacting the encapsulating polymer with a polyalkylene glycol such as PEG with amino functional termination. Triblocks can be prepared as described above using branched polyalkylene glycols with protection of groups that are not to react. Opsonization resistant carriers (microparticles/nanoparticles) can also be prepared using the techniques described

above to form sustained-release carriers (microparticles/nanoparticles) with these copolymers.

[0062] A second way to inhibit opsonization is the biomimetic approach. For example, the external region of cell membrane, known as the "glycocalyx", is dominated by glycosylated molecules which prevent non-specific adhesion of other molecules and cells. Surfactant polymers consisting of a flexible poly (vinyl amine) backbone randomly-dextran and alkanoyl (hexanoyl or lauroyl) side chains which constrain the polymer backbone to lie parallel to the substrate. Hydrated dextran side chains protrude into the aqueous phase, creating a glycocalyx-like monolayer coating which suppresses plasma protein deposition on the foreign body surface. To mimic glycocalyx, glycocalyx-like molecules can be coated on the carriers (e.g., nanoparticles or microparticles) or blended into a polymer constituting the carrier to render the treatment agent resistant to phagocytosis. An alternate biomimetic approach is to coat the carrier with, or blend in phosphorylcholine, a synthetic mimetic of phosphatidylcholine, into the polymer constituting the carrier.

[0063] For catheter delivery, a carrier comprising a treatment agent (e.g., the composition in the form of a nanoparticle or microparticle) may be suspended in a fluid for delivery through the needle, at a concentration of about one percent to about 20 percent weight by volume. In one embodiment, the loading of the treatment agent in a carrier is about 0.5 percent to about 30 percent by weight of the composition. Co-encapsulated with protein or small molecule angiogen treatment agents could be stabilizers that prolong the biological half-life of the treatment agent in the carrier upon injection into tissue. Stabilizers may also be added to impart stability to the treatment agent during encapsulation. Hydrophilic polymers such as PEG or biomimetic brush-like dextran structures or phosphorylcholine are either coated on the surface or the carrier, grafted on the surface of the carrier, blended into the polymer constituting the

carrier, or incorporated into the molecular architecture of the polymer constituting the carrier, so the carrier is resistant to phagocytosis upon injection into the target tissue location.

E. Catheter Assembly

[0064] One concern of introducing sustained-release treatment agent compositions into or adjacent blood vessels or the myocardium is that the composition remain (at least partially) at the treatment site for the desired treatment duration (e.g., two to eight weeks). Accordingly, in another embodiment, an apparatus (a catheter assembly) is described for accurately locating a treatment agent at a location in a blood vessel (preferably beyond the media layer) or in a peri-adventitial space adjacent to a blood vessel, or areas radially outward from a peri-adventitial space, or at tissue location such as the tissue of the myocardium. It is appreciated that a catheter assembly is one technique for introducing treatment agents and the following description is not intended to limit the application or placement of the treatment agent compositions described above.

[0065] Referring now to the drawings, wherein similar parts are identified by like reference numerals, **Figures 3,4, and 5** illustrate one embodiment of a delivery apparatus. In general, the delivery apparatus provides a system for delivering a substance, such as a treatment agent or a combination of treatment agents optionally presented as a sustained release composition, to or through a desired area of a blood vessel (a physiological lumen) or tissue in order to treat a localized area of the blood vessel or to treat a localized area of tissue possibly located adjacent to the blood vessel. The delivery apparatus is similar in certain respects to the delivery apparatus described in commonly-owned, U.S. Patent Application No. 09/746,498 (filed December 21, 2000), titled "Directional Needle Injection Drug Delivery Device", of Chow, et al., and incorporated herein by reference. The delivery apparatus includes a catheter assembly

300, which is intended to broadly include any medical device designed for insertion into a blood vessel or physiological lumen to permit injection and/or withdrawal of fluids, to maintain the potency of the lumen, or for any other purpose.

[0066] In one embodiment, catheter assembly 300 is defined by elongated catheter body (cannula) 312 having proximal end 313 and distal end 314. **Figure 4** shows catheter assembly 300 through line A-A' of **Figure 3** (at distal end 314). **Figure 5** shows catheter assembly 300 through line B-B' of **Figure 3** (at proximal end 313).

[0067] Referring to **Figure 3** and **Figure 4**, catheter assembly 300 includes catheter body 312 extending from proximal end 313 to distal end 314. In this example, guidewire lumen 316 is formed within catheter body 312 for allowing catheter assembly 300 to be fed and maneuvered over guidewire 318 (shown at this point within guidewire lumen 316).

[0068] Balloon 320 is incorporated at distal end 314 of catheter assembly 300 and is in fluid communication with inflation lumen 322 formed within catheter body 312 of catheter assembly 300. Balloon 320 includes balloon wall or membrane 330 which is selectively inflatable to dilate from a collapsed configuration to a desired and controlled expanded configuration. Balloon 320 can be selectively dilated (inflated) by supplying a fluid into inflation lumen 322 at a predetermined rate of pressure through inflation port 323. Balloon wall 330 is selectively deflatable, after inflation, to return to the collapsed configuration or a deflated profile. In one embodiment, balloon wall 330 can be defined by three sections, distal taper wall 332, medial working length 334, and proximal taper wall 336. In one embodiment, proximal taper wall 336 can taper at any suitable angle θ , typically between about 10° to less than about 90° , when balloon 320 is in the expanded configuration.

[0069] Distal taper wall 332, medial working length 334, and proximal taper wall 336 of balloon wall 330 can be bound together by seams or be made out of a single seamless material. Balloon 320 can be made from any suitable material, including, but not limited to, polymers and copolymers of polyolefins, polyamides, polyesters and the like. The specific material employed must be mutually compatible with the fluids employed in conjunction with balloon 320 and must be able to stand the pressures that are developed within balloon 320. Balloon wall 330 can have any suitable thickness so long as the thickness does not compromise properties that are critical for achieving optimum performance. Such properties include high burst strength, low compliance, good flexibility, high resistance to fatigue, the ability to fold, the ability to cross and re-cross a desired region of treatment or an occluded region in a lumen, and low susceptibility to defect caused by handling. By way of example, and not limitation, the thickness can be in the range of about 10 microns to about 30 microns, the diameter of balloon 320 in the expanded configuration can be in the range of about 2 millimeters (mm) to about 10 mm, and the length can be in the range of about 3 mm to about 40 mm, the specific specifications depending on the procedure for which balloon 320 is to be used and the anatomy and size of the target lumen in which balloon 320 is to be inserted.

[0070] Balloon 320 may be dilated (inflated) by the introduction of a liquid into inflation lumen 322. Liquids containing therapeutic and/or diagnostic agents may also be used to inflate balloon 320. In one embodiment, balloon 320 may be made of a material that is permeable to such therapeutic and/or diagnostic liquids. To inflate balloon 320, the fluid can be supplied into inflation lumen 322 at a predetermined pressure, for example, between about one and 20 atmospheres.

[0071] Catheter assembly 300 also includes substance delivery assembly 338A and substance for injecting a treatment agent into a tissue of a physiological

passageway. In one embodiment, delivery assembly 338A includes needle 346A having a lumen with a diameter of, for example, 0.004 inches (0.010 cm) to 0.012 inches (0.030 cm). Needle 346A is movably disposed within delivery lumen 340A formed in catheter body 312. Delivery assembly 338B includes needle 346B movably disposed within delivery lumen 340B formed in catheter body 312. Delivery lumen 340A and delivery lumen 340B each extend between distal end 314 and proximal end 313. Delivery lumen 340A and delivery lumen 340B can be made from any suitable material, such as polymers and copolymers of polyamides, polyolefins, polyurethanes, and the like. Access to the proximal end of delivery lumen 340A or delivery lumen 340B for insertion of needle 346A or 346B, respectively is provided through hub 351.

[0072] One or both of delivery lumen 340A and delivery lumen 340B may be used to deliver a treatment agent to a treatment site (e.g., through needle 346A and/or needle 346B). Alternatively, one delivery lumen (e.g., delivery lumen 340A via needle 346A) may be used to deliver a treatment agent (e.g., therapeutic angiogenic treatment agent) while the other delivery lumen (e.g., delivery lumen 340B via needle 346B) may be used to deliver a therapeutic substance that is a non-therapeutic angiogenic substance.

[0073] Catheter assembly 300 also includes an imaging assembly. Suitable imaging assemblies include ultrasonic imaging assemblies, optical imaging assemblies, such as an optical coherence tomography (OCT) assembly, magnetic resonance imaging (MRI). **Figures 3-5** illustrate an embodiment of a catheter assembly, including an OCT imaging assembly.

[0074] OCT uses short coherence length light (typically with a coherent length of about 10 to 100 microns) to illuminate the object (e.g., blood vessel or blood vessel walls). Light reflected from a region of interest within the object is combined with a coherent reference beam. Interference occurs between the two beams only when the

reference beam and reflective beam have traveled the same distance. **Figure 8** shows one suitable OCT setup similar in some respects to ones disclosed in U.S. Patent Nos. 5,465,147; 5,459,570; 5,321,501; 5,291,267; 5,365,325; and 5,202,745. A suitable optical assembly for use in conjunction with a catheter assembly is made with fiber optic components that, in one embodiment, can be passed through the guidewire lumen (e.g., guidewire lumen 316 of **Figure 3**). Light having a relatively short coherence length, l_c (given by $l_c = C/\Delta f$, where Δf is the spectral bandwidth) is produced by light source 380 (e.g., incandescent source, laser source or light emitting diode of suitable wavelength) and travels through 50/50 coupler 382 where it is divided into two paths. One path goes to blood vessel 383 to be analyzed and the other path goes to a moveable reference mirror 385. The probe beam reflected from sample 383 and the reference beam reflected from reference mirror 385 are combined at coupler 382 and sent to detector 387. The optical path traversed by the reflected probe beam and the reference beam are matched to within one coherence length such that coherent interference can occur upon recombination at coupler 382.

[0075] Phase modulator 384 produces a temporal interference pattern (beats) when recombined with the reference beam. Detector 387 measures the amplitude of the beats. The amplitude of the detected interference signal is the measure of the amount of light scattered from within a coherence gate interval 388 inside, in this case, blood vessel 383 that provides equal path lengths for the probe and reference beams. Interference is produced only for light scattered from blood vessel 383 which has traveled the same distance as light reflected from mirror 385.

[0076] In one embodiment, the optical fiber portion of the OCT imaging system can be inserted in the guidewire lumen of an over the wire catheter with guidewire lumen terminating at the imaging wire coupling. The body of the guidewire lumen (e.g., body of lumen 316 of the assembly of **Figure 3**) and the body of the balloon

assembly (e.g., body 330 of balloon assembly in **Figure 3**) should be transparent at the distal end to allow optical imaging through the body of the lumen (e.g., through the body of balloon 320). Thus, once the catheter assembly is placed, at a desired location within, for example, a blood vessel, guidewire 318 may be removed and replaced with an optical fiber. In a catheter assembly such as illustrated in **Figure 3**, the replacement of the guidewire with an optical fiber is done, in one embodiment, at low inflation pressure of balloon 320.

[0077] Where an optical fiber is substituted for a guidewire, the dimensions of a catheter does not have to be modified. Optical fibers having an outer diameter of 0.014, 0.018, or 0.032 inches (0.36, 0.46, or 0.81 mm, respectively) are suitable for current guidewire lumens. Other imaging components (e.g., fiber rotator, imaging screen, OCT system components, etc.) may be coupled to the optical fiber as it extends out hub 316 at a proximal end of the catheter assembly (e.g., at proximal end 313 of catheter assembly 300). Such components include, but are not limited to, a drive coupling that provides rotation and forward/reverse movement of the optical fiber; a detector, and an imaging screen.

[0078] **Figure 9** shows another embodiment of a catheter assembly including an OCT apparatus. In this embodiment, guidewire 3180 and optical fiber 3190 "share" common imaging lumen 3160. Imaging lumen 3160 is preferably made of a transparent material at the distal end utilized by optical fiber 3190. Catheter assembly 3000 also includes balloon 3200 with needle lumens 3400A and 3400B coupled to a proximal portion of balloon 3200.

[0079] Referring to **Figure 9**, guidewire 3180 exits imaging lumen 3160 at distal tip 3181 (i.e., distal to balloon 3200). Guidewire 3180 and optical fiber 3190 are separated in imaging lumen 3160 by plug 3185 of, for example, a polymer or copolymer material, having dimensions suitable to fill the lumen. Suitable polymers

include polyimides, polyurethanes, and polyolefins. A portion of plug 3185 may also serve as a ramp for guidewire exit port 3180. In this embodiment, imaging of a blood vessel (e.g., imaging of a wall of a blood vessel for thickness determination) is accomplished from a portion of imaging lumen corresponding with the location of balloon 3200. Thus, balloon 3200 is also preferably made of a transparent material. Flush port 3187 may also be included for clearing imaging portion of imaging lumen 3160.

[0080] At a proximal end, imaging lumen 3160 of **Figure 9** terminates in drive coupling 3195. Drive coupling 3195 provides rotation and forward/reverse direction movement of optical fiber 3190 and connection to the OCT system.

[0081] In another embodiment, the imaging assembly is based on ultrasonic technology. Ultrasonic systems are referenced in U.S. Patent Nos. 4,794,931; 5,100,185; 5,049,130; 5,485,486; 5,827,313; and 5,957,941. In one example, an ultrasonic imaging assembly, representatively including an ultrasonic transducer, may be exchanged for a guidewire through a guidewire lumen such as described above with reference to the first OCT embodiment. In another embodiment, a guidewire and ultrasonic transducer "share" a common imaging lumen similar to the embodiment described with reference to **Figure 9** and the accompanying text. In either example, imaging of, for example, a blood vessel will take place through the balloon. In the case of ultrasonic imaging, the balloon and guidewire lumen need not be transparent.

[0082] **Figures 6 and 7** are simplified sectional views of therapeutic substance delivery assembly 338A in an undeployed and deployed arrangement, respectively. Delivery lumen 340A includes distal or first section 342 and proximal or second section 344. Distal section 342 can include overhang section 347 that extends beyond opening 341 to provide a means for securing delivery lumen 340A to balloon 320. For example, overhang section 347 can be adhered along the proximal taper wall 336 and

working length 334 of balloon 320. In this manner, delivery lumen 340A is continually supported during, until, and after needle 346A is extended from delivery lumen 340A. In one embodiment, as shown in **Figure 7**, delivery lumen 340A includes bend region 350 at which distal section 342 of delivery lumen 340A is capable of bending (or generally rotating) about pivotal point 351 with respect to proximal section 344. For example, to accomplish the pivotal movement, distal section 342 of delivery lumen 340A is in contact with proximal taper wall 336 of balloon 320 (**Figure 3**).

Accordingly, in response to the inflation of balloon 320, section 342 moves relative to section 344 to form bend region 350. In one embodiment, section 342 can move from a substantially longitudinal position to a substantially perpendicular position. Thus, the angle θ of bend region 350 can vary between 0° and 90° . In one example, after inflation of balloon 320, angle θ can range from between about 10° and 90° , for example, 45° .

[0083] Needle 346A is slidably or movably disposed in delivery lumen 340A. Needle 346A includes tissue-piercing tip 352 having dispensing port 353. Dispensing port 353 is in fluid communication with a lumen (not shown) of needle 346A. In one embodiment, the lumen of needle 346A can be pre-filled with a measured amount of a treatment agent. The lumen of needle 346A connects dispensing port 353 with treatment agent injection port 359 (**Figure 3**), which is configured to be coupled to various substance dispensing means of the sort well known in the art, for example, a syringe or fluid pump. Injection port 359 allows a measured treatment agent to be dispensed from dispensing port 353 as desired or on command.

[0084] Needle 346A is coupled at proximal end 313 of catheter assembly 310 in a needle lock 355 (**Figure 3**). Needle lock 355 can be used to secure needle 346A in position once needle 346A has been either retracted and/or extended from delivery lumen 340A as described below. In one embodiment, an adjustment knob 357 can be

used to set the puncture distance of needle 346A as it is extended out from delivery lumen 340A and into the wall of the physiological lumen. For example, adjustment knob 357 may have calibrations, such that each revolution of the adjustment knob from one calibrated mark to another represents a fixed distance of travel for needle 346A. The portion of needle 346A protruding from delivery lumen 340 can be of any predetermined length, the specific length being dependent upon the desired depth of calibrated penetration and the procedure for which delivery assembly 338A is to be used. The protruding length of needle 346A can be from about 250 microns to about four centimeters (cm). It is appreciated that other mechanisms for securing needle 346A at a retracted or extended position may alternatively be used, including the incorporation of a mechanical stop optionally including a signaling (e.g., electrical signaling) device as described in commonly-owned U.S. Patent Application Serial No. 09/746,498 (filed December 21, 2000), titled "Directional Needle Injection Drug Delivery Device", and incorporated herein by reference.

[0085] Needle 346A is slidably disposed in delivery lumen 340A, so that it can move between a first retracted position (**Figure 6**) and a second extended position (**Figure 7**). In its first or retracted position, tissue-piercing tip 352 is located inboard of the distal surface of catheter body 312, so as to avoid damaging tissue during deployment of catheter assembly 310. In its second or extended position, tissue-piercing tip 352 is located outboard of the distal surface of catheter body 312, so as to permit needle tip 352 to penetrate the tissue surrounding the physiological passageway in which catheter assembly 310 is disposed.

[0086] Referring again to **Figures 6 and 7**, deflector 360 is disposed along an inner wall 362 of delivery lumen 340A. In one embodiment, deflector 360 includes distal section 370, medial section 372 and proximal section 374. In one embodiment, distal section 370 can be supported by delivery lumen 340A by bonding distal section

370 to overhang section 347 of delivery lumen 340A. Medial section 372 of deflector 360 can be disposed on inner wall 362 of delivery lumen 340A, such that as delivery lumen section 342 rotates relative to delivery section 344 to form bend region 350, deflector 360 is positioned over the outside of the curvature of bend region 350. Proximal section 374 exits out of delivery lumen 340A and is adhered to an outside wall 378 of delivery lumen 340A using an adhesive, such as glue or the like.

[0087] Deflector 360 can be any device that will provide a shield to protect the wall of delivery lumen 340A while being small enough, such that deflector 360 does not impact the track of catheter assembly 310 in any significant manner. In one embodiment, deflector 360 can be a ribbon member. The ribbon member can be made thin, flexible and resilient such that the ribbon member can move and bend as delivery lumen sections 342 and 344 bend and move relative to each other. Positioning deflector 360 of a ribbon member on the outside of the curvature of bend region 350 allows deflector 360 to shield the delivery lumen wall from piercing and the like by needle 346A as needle 346A moves through bend region 350. Deflector 360 also provides a surface upon which needle 346A can be made to track through bend region 350.

[0088] Deflector 360 is sized to fit into and along inner wall 362 of delivery lumen 340A without occluding or interfering with the ability of needle 346A to translate through bend region 350. For example, deflector 360 can have a thickness of between about 0.0005 inches (0.127 mm) and about 0.003 inches (0.762 mm). The width of deflector 360 may be between about 0.005 inches (1.27 mm) and about 0.015 inches (3.81 mm). The length of deflector 360 may be between about 1 cm and about 10 cm. Deflector 360 can be made from any suitable material, which allows deflector 360 to function, such as stainless steel, platinum, aluminum and similar alloy materials

with similar material properties. In one embodiment, deflector 360 can be made from super-elastic alloys, such as nickel titanium alloys, for example NiTi.

[0089] The catheter assembly described with reference to **Figure 3** or **Figure 9** may be used to introduce a treatment agent such as described above at a desired location. **Figure 10** illustrates one technique. **Figure 11** presents a block diagram of one technique. With reference to **Figures 10** and **11**, in a one procedure, guidewire 318 is introduced into, for example, arterial system of the patient (e.g., through the femoral artery) until the distal end of guidewire 318 is upstream of the narrowed lumen of the blood vessel (e.g., upstream of occlusion 185). Catheter assembly 300 is mounted on the proximal end of guidewire 318 and advanced over the guidewire 318 until catheter assembly 300 is position as desired. In the example shown in **Figure 10**, catheter assembly 310 is positioned so that balloon 320 and delivery lumen 340a are upstream of the narrowed lumen of LCX 170 (block 410). Angiographic or fluoroscopic techniques may be used to place catheter assembly 300. Once balloon 320 is placed and subject to low inflation pressure, guidewire 318 is removed and replaced in one embodiment with an optical fiber. In the catheter assembly shown in **Figure 9**, the imaging portion of an imaging device (e.g., OCT, ultrasonic, etc.) may be within the imaging lumen as the catheter is positioned. Once positioned, in this case upstream of occlusion 185, the imaging assembly is utilized to view the blood vessel and identify the various layers of the blood vessel (block 420).

[0090] The imaging assembly provides viewable information about the thickness or boundary of the intimal layer 110, media layer 120, and adventitial layer 130 of LCX 170 (See **Figure 1**). The imaging assembly may also be used to measure a thickness of a portion of the blood vessel wall at the location, e.g., the thickness of the various layers of LCX 170.

[0091] LCX 170 is viewed and the layer boundary is identified or a thickness of a portion of the blood vessel wall is imaged (and possibly measured), (block 140). The treatment site may be identified based on the imaging (and possibly measuring). In one example, the treatment site is a peri-adventitial site (e.g., site 190) adjacent to LCX 170. At this point, balloon 320 is dilated as shown in **Figure 7** by, for example, delivering a liquid or gas to balloon 320 through inflation lumen 322. The inflation of balloon 320 causes needle lumen 338 to move proximate to or contact the blood vessel wall adjacent to the treatment site. Needle 346A is then advanced a distance into the wall of the blood vessel (block 140). A real time image may be used to advance needle 346A. Alternatively, the advancement may be based on a measurement of the blood vessel wall or layer boundary derived from an optical image.

[0092] In the embodiment shown in **Figure 10**, needle 346A is advanced through the wall of LCX 170 to peri-adventitial site 190. Needle 346A is placed at a safe distance, determined by the measurement of a thickness of the blood vessel wall and the proximity of the exit of delivery lumen 340A to the blood vessel wall. Adjustment knob 357 may be used to accurately locate needle tip 346A in the desired peri-adventitial region. Once in position, a treatment agent, such as a treatment agent is introduced through needle 346A to the treatment site (e.g., peri-adventitial site 190).

[0093] In the above described embodiment of locating a treatment agent within or beyond a blood vessel wall (e.g., at a peri-adventitial site), it is appreciated that an opening is made in or through the blood vessel. In some instances, it may be desirable to plug or fill the opening following delivery of the treatment agent. This may be accomplished by introduction through a catheter lumen of cyanoacrylate or similar material that will harden on contact with blood.

[0094] In the above embodiment, an illustration and method was described to introduce a treatment agent at a peri-adventitial site. It is appreciated that the treatment

agent may be introduced to a portion of the wall of the blood vessel. In another embodiment, the introduction is at a point beyond the media layer (e.g., beyond media layer 120 in **Figure 1**) to the adventitial layer (e.g., adventitial layer 130 in **Figure 1**). Further, the techniques and treatment agents described may further be used to introduce a treatment agent directly into the tissue of the myocardium.

[0095] In the preceding detailed description, the invention is described with reference to specific embodiments thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader spirit and scope of the invention as set forth in the claims. The specification and drawings are, accordingly, to be regarded in an illustrative rather than a restrictive sense.